

## Analysis of Adverse Behavioral Effects of Benzodiazepines With a Discussion on Drawing Scientific Conclusions from the FDA's Spontaneous Reporting System

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The benzodiazepines can produce a wide variety of abnormal mental responses and hazardous behavioral abnormalities, including rebound anxiety and insomnia, mania and other forms of psychosis, paranoia, violence, antisocial acts, depression, and suicide. These drugs can impair cognition, especially memory, and can result in confusion. They can induce dependence and addiction. Severe withdrawal syndromes with psychosis, seizures, and death can develop. The short-acting benzodiazepines, alprazolam (Xanax) and triazolam (Halcion), are especially prone to cause psychological and behavioral abnormalities. The sources of data to support these observations and conclusions are discussed in regard to the scientific method. These adverse drug effects can wreak havoc in the lives of individuals and their families.

The benzodiazepines have for several decades been recognized in the literature and clinical practice for their capacity to cause mental and behavioral abnormalities. Alprazolam (Xanax), and to an even greater extent, triazolam (Halcion), have a significantly different profile from other benzodiazepines due to their greater capacity to bind to receptors and their shorter half-life. Triazolam's very short half-life led to the hope that it would make a particularly good sleeping medication but it has proven especially dangerous.

The brain-disabling or toxic effects of the benzodiazepines in general can be divided into several somewhat overlapping categories:

- (1) the primary clinical effect of inducing sedation (tranquility) or hypnosis (sleep), which is indistinguishable from a toxic effect except in degree;

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- (2) cognitive dysfunction, ranging from short-term memory impairment and confusion to delirium;
- (3) disinhibition (dyscontrol) or loss of impulse control, with violence toward self or others, as well as agitation, psychosis, paranoia, and depression;
- (4) withdrawal emergent symptoms, in which the individual experiences a range of symptoms from anxiety and insomnia after routine use to psychosis and seizures after the abrupt termination of long-term, larger doses;
- (5) rebound symptoms, an aspect of withdrawal, in which the individual re-experiences pre-drug symptoms — anxiety, insomnia, or other serious emotional reactions — but more intensively than before drug treatment began. Withdrawal and rebound can take place between doses, causing anxiety and other symptoms during the routine administration of benzodiazepines, especially the short-acting ones;
- (6) dependency and abuse or addiction that range along a continuum from feeling dependent on the drug to self-destructive behavior associated with drug abuse.

#### *The Mechanism of Brain-Disability*

Neurophysiological studies show that the benzodiazepines potentiate the neuronal inhibitory activity of gamma-aminobutyric acid (GABA). In doses used clinically, this results in a generalized suppression of both spontaneous and evoked electrical activity of the large neurons throughout all regions of the brain and spinal cord (Ballenger, 1995).

The binding of benzodiazepines to the GABA receptors is most concentrated in the cerebral cortex. Some high-potency benzodiazepines, such as alprazolam and triazolam, bind especially tightly to the receptor sites. This may increase their tendency to produce more intense sedation and hypnosis, and also more severe cognitive deficits, behavioral abnormalities, rebound, and withdrawal (American Psychiatric Association, 1990). Even when other benzodiazepines, such as diazepam, are given in equivalent doses, their impact on the receptor sites may not be as complete. Some advocates of the benzodiazepines have argued for a specific antianxiety effect separate from the general sedative effect, but there is no substantial evidence for this. Rall (1990) concludes “The question whether the so-called antianxiety effects of the benzodiazepines are the same as or different from the sedative and hypnotic effects has not been resolved” (p. 348). All standard antianxiety agents also have sedative effects and in my clinical experience the antianxiety effect does not occur in the absence of these effects.

People who use benzodiazepines to calm their anxiety will frequently use alcohol and other sedatives interchangeably for the same purpose, either in combination or at different times. As they switch from drug to drug, they tend to find little or no difference in the antianxiety effect. This confirms the brain-disabling principle (Breggin, 1997) that benzodiazepines have no specificity for anxiety in comparison to other sedative/hypnotic agents.

#### *The Mechanism for Producing Mental and Behavioral Abnormalities*

There are at least two probable causes for the abnormal behavior produced by benzodiazepines. One mechanism is direct suppression of CNS function, resulting in impaired executive and cognitive faculties, including impaired judgment and impulse control. Fogel and Stone (1992, p. 341) observe "Benzodiazepines, given to reduce arousal or possibly to treat a hypomanic state, may aggravate impulsive behavior by impairing the inhibition mechanism of the frontal lobes. Barbiturates may have similar effects."

Compensatory reactions within the brain following exposure to the drug can also cause severe behavioral abnormalities. Withdrawal emergent and rebound symptoms occur when a benzodiazepine is stopped between doses, or when it begins to lose its effectiveness (American Psychiatric Association, 1990). As the benzodiazepine disappears from the GABA receptor sites, the receptors may have become down-regulated (less sensitive). It is also possible that a reduction in GABA itself occurs in response to the drug, once again leaving the GABA system relatively inactive. Without the inhibiting effects of the GABA system, the "disinhibited" brain over-reacts. The American Psychiatric Association (1990) task force report, *Benzodiazepine Dependence, Toxicity, and Abuse*, theorizes that discontinuation symptoms (withdrawal emergent and rebound symptoms) arise from the abrupt withdrawal of benzodiazepines from their receptor sites. Before GABA can retake the receptor positions previously occupied by the drug, there is an acute reduction of GABA at the receptor sites, and a loss of GABA-induced inhibitory tone.

Benzodiazepine disinhibition differs in some ways from alcohol disinhibition. It can occur without a noticeable sedative intoxication, such as slurred speech, lack of coordination, or impaired alertness. Furthermore, the benzodiazepines are prescribed by a physician, often without providing the patient a warning about possible disinhibition. Unlike the experienced alcohol user, the trusting benzodiazepine user has little reason to anticipate "losing control." Expecting to be helped and not harmed by the drug, the patient is less able to understand or manage potentially overwhelming feelings of anger or violence, or other untoward emotional responses. At the time, the patient may have little idea what is driving the unfamiliar behavior, and in retrospect it may seem like a fragmented, poorly recalled nightmare.

*Adverse Reactions to the Benzodiazepines as a Group*

Standard textbooks and reviews spanning more than two decades, as well as a variety of clinical studies, confirm widespread recognition of benzodiazepine-induced behavioral abnormalities (Arana and Hyman, 1991; Ashton, 1984, 1995; DiMascio and Shader, 1970; Kochansky, Salzman, Shader, Harmatz, and Ogeltree, 1975; Maxmen, 1991; Maxmen and Ward, 1995; Rosenbaum, Woods, Groves, and Klerman, 1984; Shader and DiMascio, 1977).

Salzman, Kochansky, Shader, Porrino, Harmatz, and Swett (1974), in a placebo controlled study, found that volunteers taking chlordiazepoxide became more hostile when confronted with a situation of interpersonal frustration. In 1988, Dietch and Jennings reviewed the literature concerning reports about disinhibition whose "manifestations range from irritability to increased verbal hostility and frank assault" from many benzodiazepines (p. 184). The review found a variety of studies that demonstrate an increase in feelings of hostility or an increase in verbal hostility. However, they did not come to a definitive conclusion concerning the existence of disinhibition reactions. Reviewing the literature eighteen years later, Salzman (1992) points out the controversial nature of benzodiazepine-induced violence, but nonetheless concludes as follows: "Recent observations, however, have confirmed that hostility can be seen with all benzodiazepines, including alprazolam and clonazepam" (p. 143).

Rall (1990) summarizes the adverse behavioral effects of the benzodiazepines as follows:

*Adverse psychological effects:* Benzodiazepines may cause paradoxical effects. Nitrazepam frequently and flurazepam occasionally increase the incidence of nightmares, especially during the first week of use. Flurazepam occasionally causes garrulousness, anxiety, irritability, tachycardia, and sweating. Euphoria, restlessness, hallucinations, and hypomania behavior have been reported to occur during the use of various benzodiazepines. Antianxiety benzodiazepines have been reported to release bizarre uninhibited behavior in some users with low levels of anxiety; hostility and rage may occur in others. Paranoia, depression, and suicidal ideation occasionally also accompany the use of these agents. (p. 355)

Hobbs, Rall, and Verdoorn (1996) offer a similar description of adverse effects with the addition of amnesia to the list of symptoms that are reported to occur. Rall (1990) and Hobbs, Rall and Verdoorn believe that the paradoxical reactions are rare.

Ashton (1995) also summarizes the adverse behavioral reactions to benzodiazepines:

Benzodiazepines occasionally cause paradoxical excitement with increased anxiety, insomnia, nightmares, hypnogogic hallucinations at sleep onset, irritability, hyperac-

tive or aggressive behavior, and exacerbation of seizures in epileptics. Increased aggression, hostility, and impulsivity occur in some subjects and may result in attacks of rage and violent behavior. (p. 160)

She notes "antisocial acts, including sexual offenses and acts of violence (both homicide and suicide), have been attributed to benzodiazepines and have led to medicolegal complications" (p. 161). She states that the incidence of these adverse behavioral reactions is unknown but appears to be rare.

The APA task force report on benzodiazepines (1990, p. 18) presents a table of discontinuation symptoms that lists "anxiety, insomnia, restlessness, agitation, irritability, muscle tension" as *frequent* in their incidence. The table lists "depression" and "nightmares," as well as "lethargy" as *common but less frequent*. Clinical experience indicates that the combination of anxiety, insomnia, restlessness, agitation, irritability, nightmares, and depression can produce a spectrum of behavioral abnormalities, including suicide and violence (Breggin, 1997). Adding to the dangers, the task force's complete list of *uncommon* symptoms includes "psychosis, seizures, persistent tinnitus, confusion, paranoid delusions, hallucinations." Discontinuation symptoms can occur during interdose periods as well as after complete cessation of the drug.

#### *The Production of Mania and Rage*

As the above observations reveal, the direct effects of alprazolam and other benzodiazepines can result in adverse drug reactions of psychotic proportions. As noted in the 1996 edition of *Drug Facts and Comparisons*, the benzodiazepines as a group can cause serious psychiatric problems, including "behavior problems; hysteria; psychosis; suicidal tendencies" (p. 1441). They can disrupt central nervous system function, producing, among other things, "disorientation . . . confusion . . . delirium . . . euphoria . . . agitation." A special *Precautions* section notes "Paradoxical reactions," including "excitement, stimulation and acute rage" and "hyperexcited states, anxiety, hallucinations . . ." (p. 1440).

Mania, a psychosis, is a special danger in regard to alprazolam. The *Drug Facts and Comparisons* compendium (p. 1440) makes a specific reference to alprazolam in this regard, stating that "Anger, hostility and episodes of mania and hypomania have been noted with alprazolam." As another example, Maxmen and Ward's *Psychotropic Drug Fast Facts* (1995, p. 287) states that "manic reactions" are "Most often reported with alprazolam." It also states that "rage reactions" and "violent episodes" have especially been observed with alprazolam and diazepam (Valium). Yet another example is found in *The Handbook of Psychiatric Drug Therapy* (Hyman, Arana, and Rosenbaum, 1995,

p. 177), which singles out alprazolam to observe “Increased impulsiveness, euphoria, and frank mania have been reported with alprazolam.”

*Drug Facts and Comparisons*, *Psychotropic Drug Fast Facts* and the *Handbook of Psychiatric Drug Therapy* are intended for ready reference for physicians to alert them to adverse drug reactions. That all three indicate that mania and uncontrollable rage are special problems with alprazolam confirms my own clinical observations that this medication is more apt than others to produce these hyper-excited, aggressive states.

The FDA’s “Safety Review and Evaluation of Clinical Data” by J. Knudsen (1989) for alprazolam as a treatment for panic disorder again highlights the drug’s tendency to produce mania. In fact, it includes a review of the literature for alprazolam-induced mania. It describes several cases of mania produced in the panic disorder clinical studies and offers two tables describing fourteen cases of hypomania and one of mania. In several cases, manic attacks developed during the first week of treatment with relatively small doses of alprazolam.

#### *The Production of Depression and Suicide*

As already cited above, there are indications in the clinical literature that benzodiazepines can cause depression. Some reviews mention benzodiazepine-induced depression but express skepticism, while they nonetheless warn that the danger should be taken seriously. Arana and Hyman (1991), for example, state:

*Depression:* All benzodiazepines have been associated with the emergence or worsening of depression; whether they were causative or only failed to prevent the depression is unknown. When depression occurs during the course of benzodiazepine treatment, it is prudent to discontinue the benzodiazepine. (p. 158)

In a study of 12 patients who became addicted to therapeutic doses, Ashton (1984) maintains that “Depression was common during benzodiazepine use” (p. 1138). She also notes that benzodiazepines can blunt the emotions in general, producing “emotional anesthesia.” In a more recent paper, Ashton (1995) reports, “It is possible that benzodiazepines cause or aggravate depression, perhaps by reducing central monoamine activity” (p. 161). Reaffirming the existence of emotional anesthesia, she affirms that “Former long-term benzodiazepine users often bitterly regret their lack of emotional response to family events during the period that they were taking the drugs” (161). In most of her cases, recovery from withdrawal symptoms is incomplete, with patients continuing to report symptoms several months or more after cessation of the drug. She raises the issue of whether or not some patients suffer from irreversible changes in receptors or permanent neurological damage.

The APA task force report on benzodiazepines (1990), in a discussion of toxicity, states:

Benzodiazepines have also been reported to cause or to exacerbate symptoms of depression. This, too, is not a frequent side effect, although the depressive symptoms may be potentially serious. (p. 41)

Great Britain's Committee on Safety of Medicines recommended in 1988 that "benzodiazepines should not be used alone to treat depression or anxiety associated with depression. Suicide may be precipitated in such patients" (p. 1). Long (1990) lists depression as an adverse reaction to triazolam and alprazolam but not to diazepam. The capacity of benzodiazepines to worsen or to cause both anxiety and depression is one source of the growing interest in the role of GABAergic systems in mood disorders, including depression and mania (Bartholini, Lloyd, and Morselli, 1986; Kalpana, Musselman, Schatzberg, and Nemeroff, 1995; Paul, 1988; Roy-Byrne and Nutt, 1991).

*Cognitive, Emotional and Behavioral Abnormalities Caused by Triazolam and Alprazolam*

Several studies demonstrate rebound phenomena during the same night of the dose or during the day in association with the short-acting benzodiazepine, triazolam. Moon, Anker, and Hayes (1985) confirm that insomnia and increased daytime anxiety are problems associated with short acting benzodiazepines, such as triazolam.

De Tullio, Kirking, Zacardelli, and Kwee (1989) reviewed the charts of 72 adult male patients chronically taking triazolam for insomnia through an ambulatory Veterans Administration clinic. Thirty-nine of the patients were available for telephone interviews. Most of the patients were elderly (aged 60 or older) and almost all received a 0.25 mg. dose. Of the 39 patients interviewed, only four reported no adverse effects and 23 experienced more than one side effect. The most common effects were dizziness, rebound insomnia, and nightmares. According to the authors, "Rebound insomnia was defined as waking during the night or waking too early in the morning, and having trouble falling back to sleep" (p. 291). As a result of the study, the VA facility modified its policies on triazolam administration: "Most notably, triazolam was limited to inpatients with an automatic stop order on discharge" (p. 292).

We have already noted that the APA task force (1990) on benzodiazepines described a variety of symptoms, including depression, anxiety, hostility, and paranoia, and attributed them in part at least to discontinuation or with-

drawal. In regard to short-acting benzodiazepines, the task force made the following observations:

Abrupt discontinuation of short half-life benzodiazepines leads to rapid drug removal from the blood and brain, rapid uncovering of the receptor site, and relatively rapid onset of post-drug discontinuation syndromes . . . . Because of the severity of symptoms related to its half-life, short half-life benzodiazepines given for anxiety are frequently implicated in intense discontinuation syndromes . . . . With very short half-life drugs such as triazolam, rebound symptomatology has actually been described during the period of ingestion [i.e., during the inter-dose interval], especially when it is given nightly. (pp. 39–40)

Public and professional awareness of the special dangers of triazolam began in 1978. At that time, C. van der Kroef (1979, 1991) — a psychiatrist in the Netherlands — noticed abnormal reactions to triazolam in four of eleven patients he treated with the drug. van der Kroef describes one of his patients as follows (quoted in Dukes, 1980):

The insomnia improved at once, but psychically she rapidly went downhill. Progressively she became paranoid. Several times she asked me what the hypnotic contained — LSD perhaps? — for she felt that she was bordering on psychosis. She felt shut off from the world; it was as if she no longer belonged to society. Her friends asked her what was happening to her, so strangely was she behaving . . . . After two months I too began to suspect, particularly in light of experience with an earlier patient, that all this might be a consequence of her taking triazolam. The drug was withdrawn and replaced with nitrazepam. Within a day she felt herself again. The people around her noticed the difference and recognized her old self again. The paranoid traits, the hypermotility urge and the hyperaesthesia disappeared in the course of two days . . . . (p. V)

M.N.G. Dukes (1980) contends that all of the benzodiazepines, including those used to induce sleep (hypnotics), have been known to produce reactions that are “frankly psychotic.” While not common, according to Dukes, “virtually every known drug in this class” can produce “hallucinations, delusions, paranoia, amnesia, delirium, hypomania—almost every conceivable symptoms of psychotic madness . . .” (p. VII). According to Dukes, all the benzodiazepines used for the control of anxiety are specifically implicated in causing violence:

If one — to begin at an arbitrary point — looks to the literature for evidence that the benzodiazepines can unleash aggression then one will find it. More than a dozen papers in the literature speak of irritability, defiance, hostility, aggression, rage or a progressive development of hates and dislikes in certain patients treated with benzodiazepine tranquilizers; all those products which are widespread have been incriminated at one time or another. The phenomenon has been demonstrated in animal studies and it has even been proved possible to show in human volunteers that these drugs can release pent-up hostility, particularly in highly anxious or action-oriented individuals. (p. VII)



Until the advent of triazolam, according to Dukes, the benzodiazepines commonly used to induce sleep were not known to cause violence. We shall find his observations confirmed later by in-house studies at the FDA which indicate that Halcion — but not the older hypnotics, Dalmane (flurazepam) or Restoril (temazepam) — results in increased incidence of violent activities.

Based on clinical reports of triazolam-induced psychosis, Einarson (1980) and Einarson and Yoder (1982) confirm the possibility of a triazolam syndrome similar to that described by van der Kroef. Denson (1987) discusses a case of triazolam-induced psychosis that resulted in destruction of property and criminal charges.

R.H.B. Meyboom (1992) of the Netherlands Centre for Monitoring of Adverse Reactions to Drugs recounts the history of the Dutch experience with triazolam. He documents an outpouring of 1000 case reports to his agency concerning triazolam in 1979. He states that “despite the complexity of reactions, there were some indications of the existence of a ‘syndrome’ . . .” (p. 160). The syndrome includes anxiety and fears, agitation and aggression, depression, and paranoid ideation, as well as depersonalization and derealization, a variety of abnormal perceptions (including hyperacusis and photophobia), and amnesia. In retrospect, Meyboom believes that the syndrome results from direct toxic effects as well as withdrawal effects. Referring to the possibility of drug-induced violence and crime, he warns, “The criminal potentials of triazolam are frightening” (p. 163). Meyboom is unable to determine the frequency of these dangerous reactions.

It is difficult to demonstrate drug-induced behavioral abnormalities in highly selective, short, controlled clinical trials (see discussion below). Nonetheless, several studies confirm the hazards associated with short-acting benzodiazepines. Gardner and Cowdry (1985) found an increase in “dyscontrol” in borderline patients taking alprazolam in a double-blind, placebo-controlled crossover study. The dyscontrol includes the following behaviors: overdose, self-mutilation, head banging, jumping in front of a car, and throwing a chair at a child. Gardner and Cowdry conclude that “caution” should be exercised in regard to alprazolam, “particularly in treating individuals with a substantial history of dyscontrol” (p. 99).

Bayer, Bayer, Pathy, and Stoker (1986) conducted a nine week double-blind controlled study of triazolam and another hypnotic, chlormethiazole, in the elderly with sleep disturbances. They find daytime withdrawal effects from triazolam but not from chlormethiazole. At week three, significantly more triazolam patients are rated as more restless during the day “and they also appeared more hostile, less relaxed, more irritable and more anxious” (p. 110) compared to patients taking chlormethiazole. Patients on triazolam also have more adverse events related to the central nervous system, requiring

four of 22 patients to withdraw from the study. Three of them recovered after terminating the medication. One patient felt the tablets were "making him nervous." Other individuals developed paranoid delusions, "increasing confusion and irritability," and irrational, irritable, and uncooperative behavior.

Adam and Oswald (1989) conducted a double-blind, placebo-controlled study of triazolam and lormetazepam with forty subjects in each of the three groups. They found that "triazolam takers became more anxious on self-ratings, were judged more often to have had a bad response by an observer, more often wrote down complaints of distress, and suffered weight loss. After about ten days of regular triazolam they tended to develop panics and depression, felt unreal, and sometimes paranoid" (p. 115). According to the authors, "Subjects' written comments suggested that from about 10 days after starting triazolam, they became liable to panic attacks, feelings of despair and derealization. There were descriptions of panic episodes in public places in seven subjects during triazolam intake, but none during placebo or lormetazepam . . . . Several reported their family relationships were changed . . . . A number of triazolam subjects became paranoid . . . . Two men developed paranoid psychoses." During the withdrawal period, the anxiety of the triazolam patients "fell quickly to normal levels" (p. 118).

Soldatos, Sakkas, Bergiannaki, and Stefanis (1986) report serious adverse drug reactions in all five psychiatric inpatients during a placebo-controlled clinical trial of 0.5 mg. triazolam. Patients and nurses were blind in regard to the administration of the medication and the placebo, but the treating physicians were not. The study consisted of one week of placebo baseline, two weeks of triazolam administration, and one week of withdrawal on placebo. All five patients developed severe reactions to triazolam. Case one developed "anxiety and hallucinations on the last two days of triazolam administration and the first withdrawal day" (p. 295). Case two had a sudden increase in anxiety and became "irritable, uncooperative, and depressed." She became withdrawn and cried, and showed "considerable impairment of memory and orientation." On withdrawal of triazolam, "she became more incoherent, expressing paranoid ideas of persecution that persisted about a week." She required Haldol to control her "delusions." Case three developed severe insomnia during withdrawal and "reported considerable anxiety and irritability along with an uncontrollable fear of death, which persisted to the next day when she additionally manifested a marked degree of memory impairment." Case four, by the end of the second week of triazolam administration, became more depressed with increasing irritability and hostility. Case five, on the second week of triazolam administration, "experienced increasing daytime anxiety and he became, for the first time since admission, irritable, hostile, and somewhat guarded and paranoid towards the unit staff" (p. 296).

The authors suggest that some of the symptoms may be related to disinhibition. They warn that these serious side effects “may not be rare when triazolam is used in patients” with “major psychiatric conditions.”

Rosenbaum, Woods, Groves, and Klerman (1984) found that eight of 80 patients (ten percent) treated with alprazolam in an outpatient clinical setting develop extreme anger or hostile behavior. This is one of the highest incidences reported in the literature.

The FDA’s “Safety and Review Evaluation of Clinical Data” for alprazolam in panic disorder discusses alprazolam-induced disinhibition (Knudsen, 1989). The report states “The emergence of the rather paradoxical reaction of disinhibition often characterized by agitating, aggressive behavior, rage, hostility has been reported in patients treated with alprazolam” (p. 134). The report also describes several instances of adverse drug reactions such as “disinhibition, rage, hostility” occurring early in treatment at relatively low doses (p. 134). One physician reported three different patients as suffering from these attacks.

*Evidence from the FDA’s Spontaneous Reporting System (SRS) Concerning Benzodiazepine-Induced Adverse Drug Reactions*

In 1987, Bixler, Kales, Brubaker, and Kales, from the Sleep Research and Treatment Center and Department of Psychiatry at the Pennsylvania State University College of Medicine, reviewed adverse reactions to benzodiazepines recorded in the FDA’s spontaneous reporting system. They compared triazolam with two other benzodiazepines commonly used to induce sleep: temazepam and flurazepam. Taking into account the number and size of prescriptions for each of the three drugs, they found:

In general, triazolam had much higher overall rates than did the other two drugs. Hyperexcitability and withdrawal effects were greatest for triazolam and least for flurazepam. Amnesia was reported almost exclusively with triazolam. Rates for other cognitive as well as affective and other behavior effects were also much greater for triazolam and about equal for the other two drugs. (p. 286)

The “affective and other behavioral disturbances” category of adverse drug reactions includes “depression, psychotic depression, emotional lability, euphoria, hostility, personality disorder, and decreased libido” (p. 288).

Epidemiological studies at the FDA consistently show that alprazolam and especially triazolam produce more frequent and more serious adverse central nervous system effects, including drastic and life-threatening behavioral changes, than any other benzodiazepines. The Division of Epidemiology and Surveillance is responsible for the FDA’s spontaneous reporting system

(SRS). Most of the reports received by the agency are sent in by physicians and pharmacists concerned about possible adverse drug effects that they have observed. Bob Wise (1989b), in a working paper for the division, made an "executive summary" of reports of hostility associated with taking triazolam. Wise addresses a syndrome that "consists of anger or rage, aggression, and some actual assaults and murders." He states:

More such reports of this type have been received by FDA for triazolam and alprazolam than for any other drug product regulated by the Agency. Reporting rates, which adjust for differences in the extent of each drug's utilization, reveal much higher ratios of hostility reports to drug sales for both triazolam and alprazolam than for other benzodiazepines with similar indications.

The public health importance of these reactions lies in their severity, with occasionally lethal behavior unleashed, in the context of large population exposures as the popularity of both drugs continues to rise. (1989b, p. 1)

After a brief history of the FDA's increased focus on benzodiazepine-induced hostility, Wise explains "Our concern with such reactions then broadened to the class of triazolobenzodiazepines, when another Increased Frequency Report included a reaction in which a 57 year old woman fatally shot her mother two hours after taking one-half milligram of triazolam. When we looked at reports received during 1988, we found that triazolam's 1988 reporting rate for hostility reactions was more than twice as high as alprazolam's" (1989b, p. 2).

According to Wise (1989b):

In the entire SRS during early August, 1989, triazolam was the suspect drug in 113 reports coded as hostility, more than any other medication. It was followed by alprazolam, which accounted for 78 reports. Only nine other drugs were suspected in more than ten cases each. Another 318 drug products had fewer hostility reports, most often one (60.4 percent of 318) or two (14.8 percent). (p. 3)

Three fatalities were reported to the SRS for triazolam and one for alprazolam. Five reports of alprazolam overdose were associated with assaults, including two murders. Reactions were reported across the dose range. Males (29) and females (26) were almost evenly distributed. Furthermore, four alprazolam cases showed a reduction in hostility and rage reactions with a reduction in dose, confirming the drug's role in producing the behavior. Wise summarizes, "This apparently excessive number of rage and similar reports with triazolam and alprazolam, after adjusting the differences in frequency of drug use, provides strong suspicion that a causal relationship may obtain" (1989b, p. 12). The dose dependency seen in several cases further confirms causation.

On April 21, 1989, Wise wrote an Increased Frequency Report for the FDA on the subject of "alprazolam and rage." Wise explains that the analysis was undertaken because "Over a 12 month period, Upjohn received six

reports of rage, agitation, anger, aggression, and similar behavioral and emotional symptoms after exposures to alprazolam” (1989a, p. 1). All but one involved “manifested or verbalized murderous impulses.” According to Wise:

From spontaneous reports alone, we cannot estimate the actual incidence of alprazolam-induced rage reactions. But in light of the widely acknowledged, substantial under-reporting to spontaneous surveillance systems in general and to FDA's SRS in particular, it is entirely possible that six reports of this kind of reaction within a single year might reflect sixty or more in reality. (1989a, p. 2)

After reviewing all reports made to Upjohn and the FDA, Wise concludes:

An increase in annual frequency of “rage” reports with alprazolam promoted us to compare hostility reports more generally across several anxiolytic benzodiazepines. Alprazolam appears to have an excessive reporting rate for events coded with “hostility,” even after adjusting for differences in the extent of each drug's utilization. The numbers and potential gravity of these reactions and their possible relationship to dosage all appear to conflict with current labelling's brief description of “paradoxical effects” that occur only “in rare instances and in a random fashion.” (p. 4)

On October 17, 1988, Charles Anello, Deputy Director of the Office of Epidemiology and Biostatistics, referred to an earlier FDA comparison of spontaneous reports concerning triazolam to two other benzodiazepines used to treat insomnia, temazepam (Restoril) and flurazepam (Dalmane). The comparison found a proportionately increased number of reports of abnormal behavior in regard to triazolam. Anello comments on a further analysis comparing triazolam and temazepam, showing that for triazolam the FDA received proportionally more adverse drug reaction reports (ADRs), more serious ADRs, and more reports of five selected “behavioral” drug reactions.

On September 12, 1989, Anello authored an FDA memorandum on “Triazolam and Temazepam — Comparison Reporting Rates.” He found that adverse drug reactions were reported eleven times more frequently with triazolam than with temazepam. The relative reporting rate was 46 to 1 for amnesia, 9 to 1 for “agitation, anxiety and nervousness,” 16 to 1 for psychosis (“psychosis, hallucinations, paranoid reaction, and acute brain syndrome”), and 19 to 1 for “hostility and intentional injury.” Anello's analysis indicated that there were no convincing explanations for these differences other than actual drug effects; but he did not make a formal determination of causality.

On August 11, 1989 Paul Leber and Thomas Laughren wrote an in-house FDA memo to an upcoming Psychopharmacological Drugs Advisory Committee Meeting (PDAC). The two FDA officials stated that “Spontaneous reporting of adverse events in the United States subsequent to the marketing of triazolam has consistently revealed a pattern of excess reporting of events for Halcion compared to the two other marked benzodiazepine hypnotics.” Leber, director of the Division of Neuropharmacological

Drug Products, brought up the earlier hope that the recommendations to reduce the dose of triazolam would result in a reduction of the high rates of reported adverse behavioral reactions. However, this proved to be a false hope. Leber observed, "Halcion continues to exhibit an excess of adverse events reported compared to one comparator agent [Restoril]" in regard to "the cluster of behavioral adverse reactions."

In 1991, Diane Wysowski and David Barash, from the FDA's Division of Epidemiology and Surveillance, published a report in the *Archives of Internal Medicine*. A footnote states, "This article contains the professional views of the authors and does not constitute the official position of the Food and Drug Administration" (p. 2003). Using the FDA's spontaneous reporting system, Wysowski and Barash compared triazolam and temazepam through 1985 for "confusion, amnesia, bizarre behavior, agitation, and hallucinations." They conclude, "Considering the extent of use, reporting rates for triazolam were 22 to 99 times those for temazepam, depending upon the reaction" (p. 2003). Echoing the handwritten remarks appended to the in-house report by Anello (1989), Wysowski and Barash summarize:

Factors that indicate a causal association between triazolam and adverse behavioral reactions include corroborating case reports and sleep laboratory studies in the literature, reports of reactions in otherwise normal persons, acute onset and temporal relationship to reactions with initial dose, spontaneous recoveries and return to normalcy with drug discontinuation, and occurrences of positive rechallenge. Also, the high benzodiazepine receptor affinity with triazolam has been postulated as a possible biological mechanism. (1991, p. 2006)

While unable to "completely exclude the possibility that some selection factors are operating to produce higher reporting rates for triazolam," Wysowski and Barash found that the "evidence suggests" a greater occurrence with triazolam and than with temazepam (p. 207).

Andreadis and Schirmer (1992) responded on behalf of Upjohn with a letter to Wysowski and Barash (1992) that criticized their methodology. Mainly, Andreadis and Schirmer object to using SRS data in drawing any conclusions.

#### *American and British Responses Diverge*

Finally, in November 1991, the FDA (1992) approved new labelling for Halcion). The new label emphasizes that triazolam is indicated for short-term use, and specifies 7–10 days. Treatment lasting longer than 2 to 3 weeks requires a complete reevaluation of the patient. In addition, the label emphasizes the use of the lowest possible dose.

Here is the new warning in the Halcion label as found, for example, in the 1997 *Physicians' Desk Reference (PDR)*:

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics, including HALCION. Some of these changes may be characterized by decreased inhibition, eg, aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (eg, sedative/hypnotics). Other kinds of behavioral changes have been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines. (p. 2093)

The warning concludes with the following:

As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of HALCION. Data from several sources suggest that anterograde amnesia may occur at a higher rate with HALCION than with other benzodiazepine hypnotics. (p. 2093)

The final label change was negotiated and approved under the authority of Paul Leber, director of the division responsible for Halcion's original approval. In several ways, the label seems to fall far short of conclusions generated by both the literature and the division responsible for postmarketing surveillance.

The FDA label does mention the disproportionate reporting of amnesia; but by omission it leads the reader to believe that the behavioral effects do not occur with increased frequency. Instead of linking directly to Halcion the enormously increased risk for violence, psychosis and other extremely hazardous behavioral abnormalities, the label notes these changes have been "reported in association with the use of benzodiazepine hypnotics, including triazolam." As we documented earlier in this paper, FDA official Charles Anello noted the comparison of adverse drug reaction reports for Halcion and Restoril. For Halcion versus Restoril, the relative reporting rate for "agitation, anxiety and nervousness" was 9 to 1; for psychosis, 16 to 1; and for "hostility and intentional injury," 19 to 1.

Great Britain took a stronger stand than the FDA by banning triazolam. On October 1, 1991, the Committee on the Safety of Medicines (CSM) gave notice of the withdrawal of triazolam from the market because of concerns about safety, especially in regard to causing memory loss and depression (Asscher, 1991; Brahams, 1991). On December 9, 1991, the committee responded to Upjohn's appeal with a definitive scientific conclusion about the dangers of triazolam (p. 1). It found what it calls a clearly established causal relationship between triazolam and adverse psychiatric effects. These adverse effects occur, in the CSM's opinion, far more frequently than with other benzodiazepines. The Committee on the Safety of Medicines maintains that the spontaneous reporting system of data from the United States and England confirm or strengthen the connection between triazolam and various psychiatric side effects. Concerning the FDA epidemiological data, the

committee believes that despite differences of opinion within the FDA, the United States data provide a signal requiring further investigation (p. 10).

### *Benzodiazepines as Instruments of Suicide*

In a boxed insert entitled "Key Messages," Buckley, Dawson, Whyte, and O'Connell (1995) state, "Benzodiazepines are commonly taken in overdose and have generally been assumed to be safe." But the authors differ with that assumption of safety and conclude, "Benzodiazepines cannot be assumed to be safe in patients at risk of selfpoisoning . . ." (p. 220). Some of the tricyclic antidepressants and barbiturates are probably more toxic than benzodiazepines taken alone. But when benzodiazepines are combined with other drugs, such as alcohol, their lethality is increased.

A survey in Britain covering the decade of the 1980s demonstrated large numbers of successful suicides using benzodiazepines, alone and in combination with alcohol (Serfaty and Masterton, 1993; also see Buckley et al. 1995). Serfaty and Masterton found 891 fatalities with benzodiazepines alone and 591 in combination with alcohol. The total of all poisonings attributed to benzodiazepines was 1576 during that ten year period, putting benzodiazepines ahead of aspirin/salicylates at 1308 as well as amitriptyline [1083] and dothiepin [981]. The latter two drugs accounted for over half the fatal poisonings attributed to antidepressants.

Among the benzodiazepines, according to Serfaty and Masterton, flurazepam (Dalmane) and temazepam (Restoril) resulted in the most deaths per million prescriptions [15.0 and 11.9, respectively]. They were more dangerous than about half the antidepressants surveyed by the same methods. Triazolam (Halcion) had far fewer deaths per million prescriptions [5.1] than Dalmane or Restoril; but it was still above the mean for anxiolytic benzodiazepines [3.2].

In estimated deaths per million patients, the rank order among all benzodiazepines in Britain was dominated by the hypnotics (sleeping medications). Dalmane [90 per million] was first; Restoril [71] was second; the British hypnotic, flunitrazepam (Rohypnol) [49], was third; and Halcion was fourth [30]. Another British hypnotic, nitrazepam (Mogadon and others) [26] was fifth. In death per million patients, among the antianxiety drugs, prazepam (Centrax) [25 estimated deaths per million patients] and alprazolam (Xanax) [24] were close behind triazolam and nitrazepam.

### *Benzodiazepine-Induced Cognitive Dysfunction*

Cognitive impairment, including memory impairment and confusion, is a well-known phenomenon associated with benzodiazepines (APA, 1990;



Ashton, 1995; Golombok, Moodley, and Lader, 1988; Hommer, 1991). Alprazolam and triazolam are especially prone to produce cognitive deficits. Individuals who take triazolam to sleep on an airplane may end with a "blank" in their memories for the period surrounding the trip. Students who take benzodiazepines before exams in order to relax or to sleep are in danger of losing the material they have been studying. The same doses of triazolam produce more sedation and greater impairment of psychomotor performance in healthy elderly persons than in healthy young persons (Greenblatt, Harmatz, Shapiro, Engelhardt, Gouthro, and Shader, 1991).

#### *Effects on Sleep and the EEG*

The effects of the benzodiazepines on the EEG resemble those of other sedative-hypnotic agents, including decreased alpha activity and increased low-voltage fast activity, especially beta activity (Rall, 1990). The effects on sleep are also similar to those of other CNS depressants.

Before the brain compensates after one or more doses, the benzodiazepines decrease sleep latency (the time it takes to fall asleep) and reduce the number of awakenings. The overall time in REM sleep is usually shortened, but the number of cycles of REM may be increased later in sleep. Total sleep duration is usually increased. There are complex effects on the dream process.

Within a short time of starting triazolam, rebound begins to dominate the clinical picture, and insomnia worsens. Nishino, Mignot, and Dement (1995) note that short-acting benzodiazepines are initially preferred for elderly patients. However, they point out that "it has since been found that short-acting benzodiazepines induce rebound insomnia (a worsening of sleep beyond baseline levels on discontinuation of a hypnotic), rebound anxiety, anterograde amnesia, and even paradoxical rage" (p. 443). In general, the usefulness of benzodiazepines in insomnia is temporary at best. The drugs do not provide for normal sleep, but rather for a disruption in various aspects of the normal cycle.

#### *The Possible Production of Permanent Brain Damage*

There have been relatively few studies on the persistence of cognitive deficits following termination of benzodiazepines treatment. Despite the similar clinical and pharmacological effects of the benzodiazepines and alcohol, most reviews do not raise the issue of whether or not chronic use of benzodiazepines, like chronic use of alcohol, might cause irreversible brain damage and dysfunction. As I have previously noted (Breggin, 1991), patients on high doses of benzodiazepines develop chronic cognitive impairments

(Golombok, Moodley, and Lader, 1988; for lesser effects, see Lucki, Rickels, and Geller, 1986). But there is little literature concerning these effects. At least two reports indicate brain atrophy in association with long-term benzodiazepine use (Lader and Petursson, 1984; Schmauss and Krieg, 1987). There seem to be no follow up studies concerning these critical questions.

Ashton (1995) is one of the few reviewers to show concern about benzodiazepine-induced persistent cognitive deficits or possible brain damage. She notes the lack of studies and comments, "It remains possible that subtle, perhaps reversible, structural changes may underlie the neuropsychological impairments shown in long-term benzodiazepine users" (pp. 163–164). To date, the psychiatric profession has shown very little concern about these problems that could potentially involve millions of patients.

### *Dependence and Withdrawal*

Alcohol-like severe withdrawal symptoms from the long-term use of benzodiazepines is well-established (American Psychiatric Association, 1990). Withdrawal can develop two to twenty days after abrupt termination of the drug, depending on the half-life of the particular benzodiazepine. First signs of withdrawal may be insomnia, anxiety, agitation, irritability, and nervousness. Persistent ringing in the ears or other abnormal sounds (tinnitus) and abnormal visual perceptions may develop. Withdrawal symptoms can progress to include abdominal cramps, muscle cramps (including persistent, severe neck pain), orthostatic hypotension with fainting, nausea or vomiting, diarrhea, decreased appetite, weight loss, trembling, fever, sweats, hyperarousal and hypersensitivity to environmental stimuli, blurred vision, "buzzing" or "electricity" sensations inside the head, confusion, depersonalization, anxiety, frightening obtrusive thoughts, obsessional states, and psychosis with hallucinations, and delirium or organic brain syndrome, as well as seizures and death (Jacobs, 1995; Nishino, Mignot, and Dement, 1995; Pecknold, Swinson, Kuch, and Lewis, 1988; Silver, Yudofsky, and Hurowitz, 1994).

Most case reports suggest that even slow withdrawal may not obviate serious withdrawal symptoms. It is unclear if gradual withdrawal merely prolongs the process rather than overcoming it (Noyes, 1992).

Symptoms frequently take weeks or months to fully subside, leaving the patient with prolonged anxiety or depression (Ashton, 1995). I have seen patients who have not completely recovered from benzodiazepine withdrawal effects after many drug-free months or years. These patients typically feel irritable, fatigued, anxious, and depressed for many years, perhaps for the remainder of their lives. Large blocks of memory for the past can be eradicated, creating a sense of lost identity and alienation from self. When mem-

ories are partially recovered or when they are restimulated by photographs and by anecdotes from friends, the memories may retain a dream-like or unreal quality. Concentration, short-term memory, and sleep may be irreversibly impaired. Some of these effects may be related to persistent brain damage or dysfunction rather than to withdrawal. This may account for why some patients never fully recover from the effects of chronic benzodiazepine use. Similarly, it may account for why some patients are unable to permanently withdraw from benzodiazepines, despite repeated efforts.

Kales, Manfredi, Vgontzas, Bixler, Vela-Bueno, and Fee (1991), in a placebo-controlled sleep lab study, show that even under "brief, intermittent administration and withdrawal" of triazolam, and to a lesser extent temazepam, patients experience rebound insomnia. These withdrawal symptoms predispose the patients "to drug-taking behavior" and to increased potential for drug dependence (p. 468).

There are estimates that 50% or more of patients taking benzodiazepines in therapeutic doses over a year will become physically dependent, developing withdrawal symptoms on abrupt cessation (Ashton, 1995; Noyes, 1992; discussed in Jacobs, 1995). There is an extreme risk of withdrawal and addiction even from the short-term use of alprazolam in clinically used doses.

Among the benzodiazepines used primarily for the treatment of anxiety or panic, alprazolam seems to have an especially bad record in regard to producing withdrawal and addiction. In the field of drug addiction, alprazolam is the most frequently implicated psychiatric drug (Breggin, 1991). Often it occurs in cross-addiction with alcohol and other sedatives.

Rebound worsening of anxiety and panic afflicted many of the patients in the key studies used for FDA approval of Xanax for panic disorder (Pecknold et al., 1988). Some patients developed much more frequent panic attacks after withdrawal from the drug. Re-evaluations of the data demonstrate that many or most patients are worse off at the end of the studies than before starting the drug (Breggin, 1991; Jacobs, 1995; Marks, De Albuquerque, Cottraux, Gentile, Griest, Hand, Liberman, Relvas, Tobena, Tyrer, and Wittchen, 1989).

Some patients can find it difficult or even impossible to withdraw from as little as 0.5 mg. clonazepam each night for sleep. Even motivated patients have sometimes developed such a fear of trying to sleep without benzodiazepines that they cannot undertake a serious effort. The fear is in part psychological. But it is also based on the frightening experience of rebound insomnia and anxiety.

Physicians can mistakenly believe that increased insomnia and anxiety are caused by the patient's psychiatric disorder rather than by rebound from the drug. This error in judgment can lead physicians to prescribe benzodiazepines in ever-increasing doses. Even if the dose remains within the recommended

range, the patient can roller coaster between doses with insomnia, anxiety or other painful emotions. The patient's life can become devoted to hopeless efforts at "finding the right drug" and "taking it at the right time."

It requires a physician's patience and understanding, and often a period of many months, to wean some individuals off the benzodiazepines (for a discussion of the general principles of drug withdrawal, see Breggin and Breggin 1994). If the addiction is severe, hospitalization may be required. Unfortunately, hospitalization tends to label the patient as an "addict" or "mental patient," adding to the iatrogenic humiliation and stigmatization already experienced by the individual who struggles with drug addiction and abuse.

Even on recommended doses of 4–10 mg./day, patients may cycle from periods of excessive sedation in which they appear "drunk," to periods of hyperarousal and anxiety as they undergo partial withdrawal. Friends and family may attribute symptoms to "mental illness" until, for example, the patient begins to stumble about in a drunken manner or collapses in a stupor after one alcoholic drink during a holiday dinner. In retrospect, it will be apparent that the patient was, for months, too intoxicated to properly evaluate his or her own condition or to exercise judgment in regard to the drug effects. Often the patient's memory for the period of time will be severely impaired.

#### *Importance of Data From the FDA's Spontaneous Reporting System (MEDWATCH)*

As this review indicates, a great deal of information concerning benzodiazepine-induced adverse drug effects has been generated or confirmed by the spontaneous reporting system of the FDA (FDA, 1995; GAO, 1990). This system is based on voluntary reports, usually from pharmacists and physicians. Many of the reports are sent to the drug manufacturer, who forwards them to the FDA. Others are sent directly to the federal agency.

#### *The Limits of Pre-Marketing Studies*

Studies carried out prior to marketing a drug are not sufficient to disclose many adverse drug reactions that will later show up during the routine clinical use of the medication. The controlled studies used as the basis of approval for psychiatric drugs typically last a mere 4–6 weeks (see Breggin, 1997; Breggin and Breggin, 1994). The FDA (1995) summarizes what it calls the "Limitations of Premarketing Clinical Trials":

*Short duration* — effects that develop with chronic use or those that have a long latency period are impossible to detect

*Narrow population* — generally don't include special groups, (e.g., children, elderly), to a large degree and are not always representative of the population that may be exposed to the drug after approval

*Narrow set of indications* — those for which efficacy is being studied and don't cover actual evolving use

*Small size* (generally include 3,000 to 4,000 subjects) — effects that occur rarely are very difficult to detect. (p. 1)

While several thousand patients may be involved in the clinical trials, only one thousand or more will be involved in actual controlled studies. In addition, many of these will drop out before completion of the brief trials. The number of finishers exposed to the drug may only number in the hundreds (Breggin, 1997; Breggin and Breggin, 1994). The FDA (1995) makes the following point concerning the probability of detecting an adverse reaction:

Clinical trials are effective tools primarily designed for assessing efficacy and risk-benefit ratio, but in most cases they are neither large enough nor long enough to provide all information on a drug's safety. At the time of approval for marketing, the safety database for a new drug will often include 3,000 to 4,000 exposed individuals, an insufficient number to detect rare adverse events. For example, in order to have a 95% chance of detecting an adverse event with an incidence of 1 per 10,000 patients, an exposed population of 30,000 patients would be required. [bold type in original] (p. 1)

The director of the FDA's new MEDWATCH program, Dianne Kennedy (Kennedy and McGinnis, 1993), states:

The safety profile of a drug continually evolves over time. Clinical trials that precede product approval typically include safety data on only a few thousand patients. New information is expected to be discovered as a drug is used in larger and larger populations, in subgroups not studied during the clinical trials (e.g., pregnant women, the elderly), or in patients with numerous medical conditions taking multiple other medications. (p. 3)

In short, the clinical use of a drug can differ vastly from the controlled trials in which the drug was tested.

Writing in the *Journal of the American Medical Association* on behalf of the FDA, David Kessler (1993) declares:

Even the large, well-designed clinical trials that are conducted to gain premarket approval cannot uncover every problem than can come to light once a product is widely used . . . . If an adverse event occurs in perhaps one in 5000 or even in 1000 users, it could be missed in clinical trials but pose a serious safety problem when released to the market. (p. 2765)

Thus, the FDA does not expect a drug to be proven safe before marketing it to the public. Doctors, however, are often uninformed about this threatening

reality. The FDA has begun to make efforts to educate doctors about the frequency with which serious adverse drug effects surface for the first time during the post-marketing period (FDA, 1995; Kennedy and McGinnis, 1993; Kessler, 1993; Leber, 1992).

Although not emphasized in the comments by FDA officials, investigator bias and drug company manipulation of data also play a considerable role in the failure of clinical trials to disclose adverse drug effects. Most clinical trials are conducted by investigators who are paid by or closely aligned with the pharmaceutical industry and with biological psychiatry. There is a tendency to overlook adverse drug effects that might discourage the use of a particular medication or medications in general (Breggin, 1997; Breggin and Breggin, 1994; Moore, 1995).

#### *Drawing Scientific Conclusions from the Spontaneous Reporting System*

Reports of adverse drug effects made to the FDA or the manufacturer do not in themselves necessarily prove a causal connection between the drug and the adverse effect. To confirm causality, some of the following factors are useful:

- (1) a disproportionately high frequency of reporting or disproportionately large number of reports in comparison to other drugs, especially in the same or similar class of drugs;
- (2) a meaningful or strong enough association as reflected in epidemiological and clinical data;
- (3) an absence of alternative explanations for the increased frequency or number of reports;
- (4) reports indicating a temporal relationship between the adverse reactions and initial doses of the drug or increased doses of the drug;
- (5) reports of dose-dependent reactions, that is, increased frequency or numbers of adverse reactions with higher dosages;
- (6) reports of positive dechallenge — resolution of the reaction following drug withdrawal;
- (7) reports of positive rechallenge — the reaction is provoked once again by resuming the drug;
- (8) reports of adverse reactions in individuals;
- (9) corroborating clinical experience (published and unpublished);
- (10) data from clinical trials, including controlled trials;
- (11) a rational medical and/or neurochemical explanation for a causal connection between the drug and the adverse reaction, and the corresponding absence of a better explanation.

The Federal Judicial Center (Bailey, Gordis, Green, and Rothstein, 1994) has proposed a series of criteria that compact many of the above points.

Drawing on Koch's postulates, the authors of the report state that "seven factors should be considered when an epidemiologist determines whether the association between an agent and a disease is causal." Put in the form of questions, they list the following factors:

1. How strong is the association between the exposure and disease?
2. Is there a temporal relationship?
3. Is the association consistent with other research?
4. Is the association biologically plausible (consistent with existing knowledge)?
5. Have alternative explanations been ruled out?
6. Does the association exhibit specificity?
7. Is there a dose-response relationship? (p. 124)

None of the above individual criteria is an absolute requirement for coming to a reasonable or scientific conclusion. One must weigh the best available evidence and come to as sound a conclusion as possible in the interest of medicine, science, and public safety. Commonly or even typically, decisions with a high degree of probability will be made with an incomplete set of data.

#### *The Impact of the Spontaneous Reporting System*

While it would be helpful to have confirmation from controlled clinical trials, it is typically impossible to demonstrate many known or proven adverse drug reactions through controlled clinical trials (FDA, 1995; GAO, 1990; Kennedy and McGinnis, 1993; Kessler, 1993; Leber, 1992; reviewed in Breggin, 1997). Negative findings from controlled clinical trials involving a drug cannot be used to rule out a causal connection between a drug and an adverse reaction. In fact, the vast majority of changes in drug labelling made during the post-marketing phase is based on the kind of data that is generated by the spontaneous reporting system and almost none of the changes result from controlled clinical trials. Even when drugs are taken off the market, the FDA often acts on the basis of spontaneous reports.

In describing the impact of the spontaneous reporting system, Kessler (1993), states:

In response to voluntary reports from physicians to the FDA or the manufacturer, the FDA has issued warnings, made label changes, required manufacturers to conduct post-marketing studies, and ordered product withdrawals that have ultimately prevented patient deaths and suffering. (p. 2765)

The FDA (FDA, 1995) itself makes clear that the spontaneous reporting system is the most important source of postmarketing information on adverse drug reactions. It frequently leads to scientific determinations for the need to modify drug labels or to withdraw drugs from the market.

According to a 1990 Government Accounting Office (GAO) report, more than 50% of all drugs approved by the FDA between 1976 and 1985 were found during postmarketing to have previously undetected “serious” side effects, sometimes requiring removal from the market. Fifteen psychopharmaceuticals were approved during this period, nine of which were found during postmarketing to have serious risks, leading in one case to removal from the market (p. 25, pp. 74–78). The antidepressant nomifensine was found to cause massive intravascular hemolytic anemia—but only after it had been on the market worldwide for eight or nine years (Leber, 1992, p. 6).

These observations indicate that controlled clinical trials are not the most significant scientific method for determining causality in regard to adverse drug reactions. I have reviewed the entire list of serious adverse reactions to psychiatric drugs detected during the postmarketing period in the GAO study. It seems probable that every one of them was discovered and confirmed through a combination of the spontaneous reporting system and general clinical experience. There is no evidence that any of these adverse reactions was primarily identified or even confirmed by means of a controlled clinical trial.

#### *The Severity of the Consequences*

The severity of the psychological, occupational, and social consequences of benzodiazepine toxicity and withdrawal problems are rarely if ever adequately addressed in the psychiatric literature (discussed in Jacobs, 1995). In my clinical and forensic medical experience, individuals under the influence of benzodiazepines can commit crimes involving fraud and violence that are wholly out of character for them. Family assets and family life may be sacrificed to drug abuse and addiction. David Jacobs (1995) points out that many psychiatrists seem too indifferent toward adverse drug effects. He notes that in medical and scientific papers, adverse drug reactions are usually reported as isolated events that do not impinge upon other people and upon the individual’s overall life. Jacobs (1997) maintains:

Many people tacitly assume that when a person experiences an adverse drug reaction, he or she can and will simply stop taking the medication, thus terminating the adverse drug reaction. The picture when it comes to the benzodiazepines is commonly very different. (p. 1)

As Jacobs observes, the consequences of continuous benzodiazepine use — such as lethargy, emotional flatness, disinhibition, depression, and a worsening of anxiety — are not likely to be understood as drug-related by patients, their families, or their physicians. When patients try to reduce or stop the



medication, they do not realize that their increased insomnia or anxiety are a result of rebound. The patient's personal and work relationships may deteriorate due to physical, cognitive and emotional problems induced by the drug. Withdrawal can be experienced as torture, and the effects of withdrawal can disrupt social and occupational life. Rage, mania and other drug-induced reactions that reach psychotic proportions can ruin lives and wreck havoc among loved ones and innocent bystanders.

## References

- Adam, K., and Oswald, I. (1989). Can a rapidly-eliminated hypnotic cause daytime anxiety? *Pharmakopsychiatrie*, 22, 115–119.
- American Psychiatric Association. (1990). *Benzodiazepine dependence, toxicity, and abuse*. Washington, D.C.: American Psychiatric Association.
- Andreadis, N.A., and Schirmer, R.G. (1992). Use of spontaneous reporting system data. *Archives of Internal Medicine*, 152, 1527–1529.
- Anello, C. (1988, October 17). Memorandum to Director, Division of Neuropharmacological Drugs. Subject triazolam (Halcion). FDA Office of Epidemiology and Biostatistics, Rockville, Maryland. Obtained through the Freedom of Information Act.
- Anello, C. (1989, September 12). Memorandum: Triazolam and temazepam—Comparison reporting rates. FDA Center for Drug Evaluation and Research, Office of Epidemiology and Biostatistics, Rockville, Maryland. Obtained through the Freedom of Information Act.
- Arana, G., and Hyman, S. (1991). *Handbook of psychiatric drug treatment* (second edition). Boston: Little, Brown and Company.
- Ashton, H. (1984). Benzodiazepine withdrawal: An unfinished story. *British Medical Journal*, 288, 1135–1140.
- Ashton, H. (1995). Toxicity and adverse consequences of benzodiazepine use. *Psychiatric Annals*, 25, 158–165.
- Asscher, A.W. (1991, October 1). [Letter] Dear doctor/dentist/pharmacist: Withdrawal of triazolam. London, England: Committee on Safety of Medicines.
- Ayd, F.J. (1992, May). Triazolam 0.25 mg: A reappraisal. *International Drug Therapy Newsletter*, 27(5), 17–24.
- Bailey, L., Gordis, L., Green, M., and Rothstein, P. (1994). Reference guide on epidemiology. *Federal Judicial Center's reference manual on scientific evidence* (pp. 122–170). St. Paul, Minnesota: West Publishing Company.
- Ballenger, J. (1995). Benzodiazepines. In A. Schatzberg and C. Nemeroff (Eds.), *The American Psychiatric Press textbook of psychopharmacology* (pp. 215–230). Washington, D.C.: American Psychiatric Press.
- Bartholini, G., Lloyd K., and Morselli, P. (Eds.). (1986). GABA and mood disorders: Experimental and clinical research. New York: Raven.
- Bayer, A.J., Bayer, E.M., Pathy, M.S.J., and Stoker, M.J. (1986). A double-blind controlled study of chlormethiazole and triazolam as hypnotics in the elderly. *Acta Psychiatrica Scandinavica*, 73 (supplement 329), 104–111.
- Bixler, E.O., Kales, A., Brubaker, B.H., and Kales, J.D. (1987). Adverse reactions to benzodiazepine hypnotics: Spontaneous reporting system. *Pharmacology*, 35, 286–300.
- Brahams, D. (1991, October 12). Triazolam suspended. *Lancet*, 338, 938.
- Breggin, P.R. (1991). *Toxic psychiatry: Why therapy, empathy and love must replace the drugs, electroshock and biochemical theories of the "new psychiatry."* New York: St. Martin's Press.
- Breggin, P.R. (1997). *Brain-disabling treatments in psychiatry: Drugs, electroshock, and the role of the FDA*. New York: Springer Publishing Company.
- Breggin, P.R., and Breggin, G. (1994). *Talking back to Prozac: What doctors aren't telling you about today's most controversial drug*. New York: St. Martin's Press.

- Buckley, N.A., Dawson, A.H., Whyte, I.M., and O'Connell, D.L. (1995, January 28). Relative toxicity of benzodiazepines in overdose. *British Medical Journal*, 310, 219–220.
- Byck, R. (1975). Drugs and the treatment of psychiatric disorders. In L.S. Goodman and A. Gilman (Eds.), *The pharmacological basis of therapeutics* (fifth edition, pp. 152–200). New York: Macmillan.
- Committee on Safety of Medicines. (1988). Benzodiazepines, dependence and withdrawal symptoms. *Current Problems*, 21, 1–2.
- Committee on Safety of Medicines. (1991). Triazolam: Assessor's report. Appeal by Upjohn against revocation of product license. London, England: Author.
- Denson, R. (1987). Involuntary self-intoxication with triazolam. *Psychiatric Journal of the University of Ottawa*, 12, 242–243.
- De Tullio, P.L., Kirking, D.M., Zacardelli, D.K., and Kwee, P. (1989, April). Evaluation of long-term triazolam use in an ambulatory veterans administration medical center population. *DICP, The Annals of Pharmacotherapy*, 23, 290–293.
- Dietch, J.T., and Jennings, R.K. (1988, May). Aggressive dyscontrol in patients treated with benzodiazepines. *Journal of Clinical Psychiatry*, 49(5), 184–187.
- DiMascio, A. (1970). Behavioral toxicity. In A. DiMascio and R. Shader (Eds.), *Clinical handbook of psychopharmacology* (pp. 185–194). New York: Science House.
- DiMascio, A., and Shader, R.I. (Eds.). (1970). *Clinical handbook of psychopharmacology*. New York: Science House.
- Division of Epidemiology and Surveillance, Office of Epidemiology and Biostatistics. (1990, March 20). Memorandum: Increased Frequency Report: Triazolam deaths, interaction with alcohol, and CNS depression. FDA Center for Drug Evaluation and Research. Obtained through the Freedom of Information Act.
- Drug Facts and Comparisons*. (1996). St. Louis: Facts and Comparisons.
- Dukes, M.N.G. (1980). The van der Kroef syndrome. In M.N.G. Dukes (Ed.), *Side effects of drugs, Annual 4* (pp. V–IX). Amsterdam: Excerpta Medica.
- Einarson, T. R. (1980). Hallucinations from triazolam. *Drug Intelligence & Clinical Pharmacy*, 14, 714–715.
- Einarson, T. R., and Yoder, E.S. (1982). Triazolam psychosis: A syndrome? *Drug Intelligence & Clinical Pharmacy*, 16, 330.
- Fogel, B.S., and Stone, A.B. (1992). Practical pathophysiology in neuropsychiatry: A clinical approach to depression and impulsive behavior in neurological patients. In S.C. Yudofsky and R.E. Hales (Eds.), *American Psychiatric Press textbook of psychiatry* (pp. 329–344). Washington, D.C.: American Psychiatric Press.
- FDA (Food and Drug Administration). (1992, April). New Halcion labeling. *Medical Bulletin*, 22(1), 7.
- FDA (Food and Drug Administration). (1995, June). Clinical therapeutics and the recognition of drug-induced disease. A MEDWATCH continuing education article. Rockville, Maryland: Center for Drug Evaluation and Research, Food and Drug Administration. Obtained through the Freedom of Information Act.
- French, A. (1989). Dangerous aggressive behavior as a side effect of alprazolam. *American Journal of Psychiatry*, 146, 276.
- GAO (Government Accounting Office). (1990, April). FDA drug review: Postapproval risks 1976–1985. Report to the Chairman, Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Operations, House of Representatives.
- Gardner, D.L., and Cowdry, R.W. (1985, January). Alprazolam-induced dyscontrol in borderline personality disorder. *American Journal of Psychiatry*, 142, 98–100.
- Gold, M., Miller, N., Stennie, K., and Populla-Vardi, C. (1995). Epidemiology of benzodiazepine use and dependence. *Psychiatric Annals*, 25, 146–148.
- Golombok, S., Moodley, P., and Lader, M. (1988). Cognitive impairment in long-term benzodiazepine users. *Psychological Medicine*, 18, 365–374.
- Greenblatt, D.J., Harmatz, J.S., Shapiro, L., Engelhardt, N., Gouthro, T.A., and Shader, R.I. (1991). Sensitivity to triazolam in the elderly. *New England Journal of Medicine*, 324, 1691–1698.

- Hobbs, W., Rall, T., and Verdoorn, T. (1996). Hypnotics and sedatives: Ethanol. In J. Hardman and L. Limbird (Eds.), *The pharmacological basis of therapeutics* (ninth edition, pp. 361–397). New York: McGraw-Hill.
- Hommer, D. (1991). Benzodiazepines: Cognitive and psychomotor effects. In P. Roy-Byrne and D. Cowley (Eds.), *Benzodiazepines in clinical practice: Risks and benefits* (pp. 111–130). Washington, D.C.: American Psychiatric Press.
- Hyman, S., Arana, G., and Rosenbaum, J. (1995). *Handbook of psychiatric drug therapy* (third edition). New York: Little, Brown.
- Jacobs, D.H. (1995). Psychiatric drugging: Forty years of pseudo-science, self-interest, and indifference to harm. *Journal of Mind and Behavior*, 16, 421–470.
- Jacobs, D.H. (1997, February 26). Personal communication.
- Kales, A. (1991, September). An overview of safety problems of triazolam. *International Drug Therapy Newsletter*, 26(7), 25–28.
- Kales, A., Bixler, E.O., and Vgontzas, A.N. (1993, September 4). The evidence against is extensive and consistent. *British Medical Journal*, 307, 626.
- Kales, A., Manfredi, R.L., Vgontzas, A.N., Bixler, E.O., Vela-Bueno, A., and Fee, E.C. (1991, April). Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. *Clinical Pharmacology and Therapeutics*, 49, 468–476.
- Kales, A., Scharf, M.B., and Kales, J.D. (1978, September 15). Rebound insomnia: A new clinical syndrome. *Science*, 201, 1039–1041.
- Kales, A., Soldatos, C.R., Bixler, E.O., and Kales, J.D. (1983). Rebound insomnia and rebound anxiety: A review. *Pharmacology*, 26, 121–137.
- Kalpana, N., Musselman, D., Schatzberg, A. and Nemeroff, C. (1995). Biology of mood disorders. In A. Schatzberg and C. Nemeroff (Eds.), *The American Psychiatric Press textbook of psychopharmacology* (pp. 439–478). Washington, D.C.: American Psychiatric Press.
- Kennedy, D.L., and McGinnis, T. (1993, September). *Monitoring adverse drug reactions: The FDA's new MEDWATCH program*, P and T. Rockville, Maryland: Food and Drug Administration. Obtained through the Freedom of Information Act.
- Kessler, D. (1993). Introducing MEDWATCH: A new approach to reporting medication and device adverse effects and product problems. *Journal of the American Medical Association*, 269, 2765–2768.
- Knudsen, J. (1989, March 24). Safety review and evaluation of clinical data for Xanax for the treatment of panic disorders. Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, Maryland. Obtained through the Freedom of Information Act.
- Kochansky, G.E., Salzman, C., Shader, R.I., Harmatz, J.S., and Ogeltree, A.M. (1975, August). The differential effects of chlordiazepoxide and oxazepam on hostility in a small group setting. *American Journal of Psychiatry*, 132, 861–863.
- Kostowski, W. (1978). Effects of sedatives and major tranquilizers in aggressive behavior. *Modern Problems in Pharmacopsychiatry*, 13, 1–12.
- Lader, M. (1993). Neuroleptic-induced deficit syndrome. *Journal of Clinical Psychiatry*, 54, 493–500.
- Lader, M., and Petursson, H. (1984). Computed axial brain tomography in long-term benzodiazepine users. *Psychological Medicine*, 14, 203–206.
- Leber, P. (1992). Postmarketing surveillance of adverse drug effects. In J. Kane and J. Lieberman (Eds.), *Adverse effects of psychotropic drugs* (pp. 3–12). New York: Guilford Press.
- Leber, P., and Laughren, T. (1989, August 11). Background comments to 31st meeting of the Psychopharmacological Drugs Advisory Committee (PDAC), September 21 and 22, 1989. Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, Maryland. Obtained through the Freedom of Information Act.
- Long, J.W. (1990). *The essential guide to prescription drugs*. New York: Harper & Row.
- Lucki, I., Rickels, K., and Geller, A. (1986). Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology*, 88, 426–433.
- Marcus, L., Plasky, P., and Salzman, C. (1988). Effects of psychotropic drugs on memory: Part I. *Hospital and Community Psychiatry*, 39, 255–256.

- Marks, I.M., De Albuquerque, A., Cottraux, J., Gentile, V., Griest, J., Hand, I., Liberman, R.L., Relvas, J.S., Tobena, A., Tyrer, P., and Wittchen, H.-U. (1989). The "efficacy" of alprazolam in panic disorder and agoraphobia. A critique of recent reports [letter]. *Archives of General Psychiatry*, 46, 668-669.
- Maxmen, J. (1991). *Psychotropic drugs fast facts*. New York: W.W. Norton.
- Maxmen, J., and Ward, N. (1995). *Psychotropic drugs fast facts*. New York: W.W. Norton.
- Meyboom, R.H.B. (1992). The triazolam experience in 1979 in the Netherlands. A problem of signal generation and verification. In B. Strom and G. Velo (Eds.), *Drug epidemiology and post-marketing surveillance* (pp. 159-167). New York: Plenum Press.
- Moon, C.A.L., Ankier, S.I., and Hayes, G. (1985, September). Early morning insomnia and daytime anxiety — A multicentre general practice study comparing loprazolam and triazolam. *British Journal of Clinical Practice*, 39, 352-358.
- Moore, T. (1995). *Deadly medicine: Why tens of thousands of heart patients died in America's worst drug disaster*. New York: Simon & Schuster.
- Nishino, S., Mignot, E., and Dement, W. (1995). Sedative-hypnotics. In A. Schatzberg and C. Nemeroff (Eds.), *American Psychiatric Press textbook of psychopharmacology* (pp. 405-416). Washington, D.C.: American Psychiatric Press.
- Noyes, R. (1992, February). Discontinuing benzodiazepine use in anxiety disorder patients. *Psychiatric Times*, p. 39.
- O'Donovan, M.C., and McGuffin, P. (1993, April 10). Short acting benzodiazepines. *British Medical Journal*, 306, 945-946.
- Oswald, I. (1991, August 24). Safety of Triazolam. *Lancet*, 338, 516-517.
- Paul, S. (1988). Anxiety and depression: A common neurobiologic substrate? *Journal of Clinical Psychiatry*, 49 (supplement), 13-16.
- Pecknold, J.C., Swinson, R.P., Kuch, K., and Lewis, C.P. (1988). Alprazolam in panic disorder and agoraphobia. Results from multicenter trial. III. Discontinuation effects. *Archives of General Psychiatry*, 45, 429-436.
- Physicians' Desk Reference*. (1997). Montvale, New Jersey: Medical Economics.
- Rall, T.W. (1990). Hypnotics and sedatives: Ethanol. In A. Gilman, T. Rall, A. Nies, and P. Taylor (Eds.), *The pharmacological basis of therapeutics* (eighth edition, pp. 345-382). New York: McGraw-Hill.
- Rosenbaum, J.E., Woods, S.W., Groves, J.E., and Klerman, G. (1984). Emergence of hostility during alprazolam treatment. *American Journal of Psychiatry*, 141, 792-793.
- Roy-Byrne, P., and Nutt, D. (1991). Benzodiazepines: Biological mechanisms. In P. Roy-Byrne and D. Cowley (Eds.), *Benzodiazepines in clinical practice: Risks and benefits* (pp. 3-18). Washington, D.C.: American Psychiatric Press.
- Salzman, C. (1992). Behavioral side effects of benzodiazepines. In J.M. Kane and J.A. Lieberman (Eds.), *Adverse effects of psychotropic drugs* (pp. 139-152). New York: Guilford Press.
- Salzman, C., Kochansky, G.E., Shader, R.I., Porrino, L.J., Harmatz, J.S., and Swett, Jr., C.P. (1974, September). Chlordiazepoxide-induced hostility in a small group setting. *Archives of General Psychiatry*, 31, 401-405.
- Schmauss, C., and Krieg, J.-C. (1987). Enlargement of cerebral fluid spaces in long-term benzodiazepine abusers. *Psychological Medicine*, 17, 869-873.
- Serfaty, M., and Masterton, G. (1993). Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *British Journal of Psychiatry*, 163, 386-393.
- Shader, R., and DiMascio, A. (1977). *Psychotropic drug side effects*. Huntington, New York: Robert E. Krieger Publishing Company.
- Silver, J.M., Yudofsky, S.C., and Hurowitz, G.I. (1994). Psychopharmacology and electroconvulsive therapy. In S.C. Yudofsky and R.E. Hales (Eds.), *American Psychiatric Press textbook of psychiatry* (pp. 897-1007). Washington, D.C.: American Psychiatric Press.
- Soldatos, C.R., Sakkas, P.N., Bergiannaki, J.D., and Stefanis, C.N. (1986, April). Behavioral side effects of triazolam in psychiatric inpatients: Report of five cases. *Drug Intelligence & Clinical Pharmacy*, 20, 294-297.

- van der Kroef, C. (1979, September 8). Reactions to triazolam. *Lancet*, 526.
- van der Kroef, C. (1991, July 6). Triazolam. *Lancet*, 338, 56.
- Wise, B. (1989a, April 21). Increased Frequency Report (IFR): Alprazolam and rage. FDA Division of Epidemiology and Surveillance, Rockville, Maryland. Obtained through the Freedom of Information.
- Wise, B. (1989b, September 19). Reports of Hostility After Exposure to Triazolobenzodiazepines (working paper). FDA Division of Epidemiology and Surveillance, Rockville, Maryland. Obtained through the Freedom of Information Act.
- Wysowski, D.K., and Barash, D. (1991, October). Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's spontaneous reporting system. *Archives of Internal Medicine*, 151, 2003–2008.